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Perspectives CME

Topics in Antiviral Medicine™

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Topics in Antiviral Medicine™

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Perspectives

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The IAS–USA offers this state-of-the-art activity as part of a nationwide CME effort for physicians on the evolving challenges of managing HIV disease.

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On completion of this activity, the learner will be able to:

- Define barriers to linkage, engagement, and retention in HIV care experienced by vulnerable patient populations
- Discuss aspects of the Patient Protection and Affordable Care Act that may affect HIV-infected individuals in the United States
- Describe the effects of persistent immune activation in HIV infection

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This enduring material is designed for physicians who are actively involved in the medical care of people with HIV infection, specifically those who:

- Have a solid, working knowledge of HIV disease management
- Provide comprehensive or specialty care for patients with HIV infection
- Are currently active in HIV research

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

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Improving the Management of HIV Disease®

The annual full-day advanced CME courses continue to focus on cutting-edge, scientifically rigorous issues presented by leading experts in the field, providing the latest insights and data on the full spectrum of HIV- and AIDS-related treatment issues.

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Tuesday, March 18, 2014
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Atlanta, Georgia
Tuesday, April 1, 2014
Cobb Galleria

Los Angeles, California
Wednesday, April 23, 2014
The Westin Bonaventure

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Friday, March 21, 2014
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Monday, April 14, 2014
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Perspective

Immune Activation, HIV Persistence, and the Cure

HIV infection is characterized by persistent immune activation, even in the context of suppressive antiretroviral therapy. This persistent activation, which appears to be fueled by microbial translocation from the gut resulting from HIV-related damage, is associated with deficits in immune function that in turn contribute to persistent activation. The presence of latent HIV reservoirs in lymphoid tissues also provokes immune activation in the context of immune suppression, resulting in expansion of the viral reservoir and potential viral replication, even with suppressive antiretroviral therapy. Therapeutic strategies are being devised to reduce persistent immune activation and limit the size of the HIV reservoir. This article summarizes a presentation by Daniel C. Douek, MD, PhD, at the IAS–USA continuing education program held in San Francisco, California, in March 2013.

Keywords: *HIV, immune activation, persistence, gut, microbial translocation, reservoir, raltegravir intensification, lymphoid tissue*

Viral infection is accompanied by an innate immune response during the acute phase of infection. For most types of viral infection, immune activation is reduced as the immune response acts to reduce viral load. In HIV infection, however, immune activation persists despite the initial decline in viral load. Persistent activation is observed in numerous components of the innate immune system, including cells (eg, activated phenotypes of macrophages and dendritic cells), cytokines and chemokines (tumor necrosis factor, interleukin [IL]-1, IL-6, IL-8, IL-15, and IL-10), acute phase proteins (serum amyloid A, C-reactive protein), elements of the coagulation cascade (D-dimers, tissue factor), elements of fibrosis (matrix metalloproteinase activation, collagen deposition), and microbial sensors (lipopolysaccharide binding protein, soluble CD14). In the adaptive immune system, there is increased turnover and exhaustion of T cells, low thymic output, and establishment of a viral reservoir. Similarly, there is increased turnover of B cells, an altered phenotypic profile, and hyperimmunoglobulinemia.

With regard to the causes of chronic immune activation in HIV infection, it does not appear that HIV alone can account for the persistence of immune activation. In HIV infection, viral load is a poor predictor of disease progression, whereas measures of immune activation, including the frequency of activated T cells, are independent predictors of progression. Elite controllers—individuals who, in the absence of therapy, spontaneously control viral replication to undetectable levels—exhibit high levels of activated CD38+ CD8+ T cells on progression.[1] Further, when viral load is suppressed with antiretroviral therapy, immune activation persists and is predictive of disease progression. Potential contributors to chronic immune activation include increased antigen load, bacterial overgrowth, the presence of herpes viruses, and translocation of proinflammatory mediators across the gut mucosa.

Consequences of HIV Infection in the Gastrointestinal Tract

A healthy gut is characterized by tight epithelial junctions and a layer of mucus (Figure 1). Antimicrobial peptides and large quantities of antibodies are secreted into the lumen. The majority of CD4+ T cells in the body is contained in the gut. Cross-communication occurs between microbes and epithelial cells or immune cells as part of a complex system that protects what is essentially the greatest surface area of tissue in contact with the outside environment. In HIV infection, there is a massive loss of CD4+ T cells in the gut during acute infection, with enteropathy caused by enterocyte apoptosis and a 2- to 10-fold increased permeability (leakiness) of the gut. Gut permeability allows translocation of microbial products into the systemic circulation, causing systemic immune activation.

The emerging picture of the role of microbial translocation from the gut in fueling persistent immune activation is of a cyclic process in which more activated T cells are produced, providing more target cells for HIV, and resulting in immune deficiency via increased infection of the T cells, low thymic output, lymphoid tissue fibrosis, and T and B cell dysfunction (Figure 2). Increased immune deficiency results in persistent microbial translocation and poor pathogen control, allowing other viruses (eg, cytomegalovirus) and bacteria to replicate and further priming immune activation. Ongoing immune activation results in systemic inflammation, tissue damage (including fibrosis of lymphoid tissue) in the heart, lungs, liver, and kidneys, and coagulopathy, all of which are associated with non–HIV-related morbidity and mortality. By controlling HIV replication, antiretroviral therapy subdues some of these processes and allows recovery of some T cell populations. However, it does not stop immune activation, resultant inflammation, or tissue damage completely.

As shown by Hunt and colleagues,[1,2] T cell activation does decline during antiretroviral therapy but remains at higher than normal levels even after many years of viral suppression. The higher the level of immune activation (indicated by the percentage of

Dr Douek is Chief of the Human Immunology Section at the National Institutes of Health in Bethesda, Maryland. Dr Douek's presentation for the IAS–USA was performed in the capacity of a private citizen and does not necessarily reflect the views of the US government.

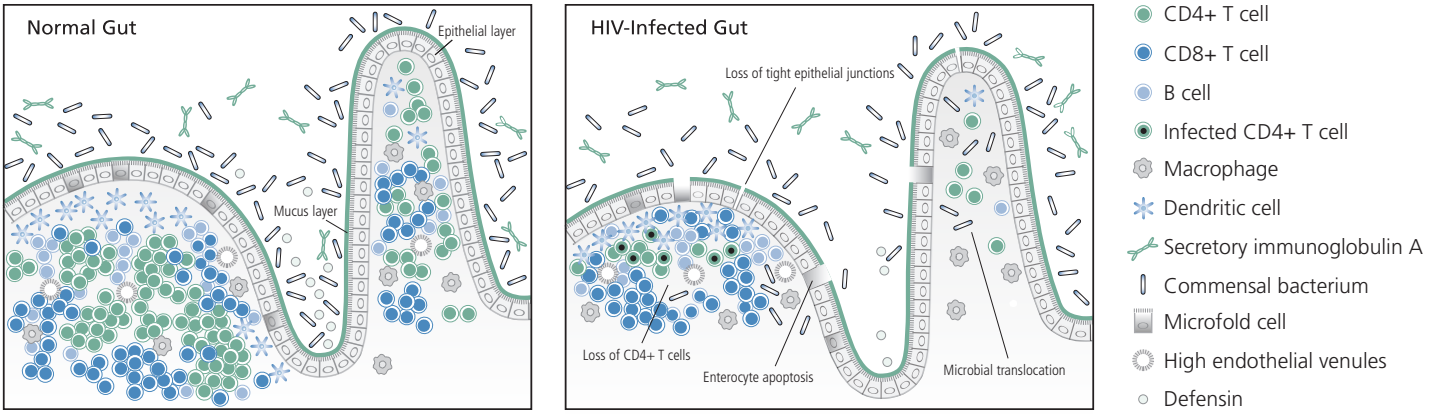

Figure 1. The effects of HIV infection in the gastrointestinal tract. Adapted from Mowat,[12] and Brenchley and Douek.[13]

activated CD38+ CD8+ T cells persisting during antiretroviral therapy), the lower the recovery of CD4+ T cell levels. Overall, these investigators have shown that numerous markers of inflammation and gut barrier dysfunction are associated with an increased risk of mortality among HIV-infected patients, independent of CD4 + cell count and viral load (Figure 3).[3] For example, elevated blood levels of intestinal fatty acid binding protein (iFABP), a marker of damage in the gut epithelial lining, are associated with an 8-fold increased risk of mortality among HIV-infected patients.

Immune Activation and HIV Persistence

In addition to the other deleterious effects noted, persistent inflammation appears to be associated with the persistence of HIV. Ongoing HIV replication in host reservoirs also appears to contribute to persistent inflammation. Research is under way to determine whether novel investigational approaches can reduce HIV reservoir size, through, for example, the use of antiinflammatory drugs or by enhancement of HIV-specific immunity.

An association between HIV persistence and persistent immune activation in patients with undetectable plasma HIV RNA levels has been shown in studies of raltegravir intensification. In one study, antiretroviral therapy with raltegravir intensification resulted in a substantially greater reduction in immune activation (higher percentage of CD38+ memory CD8+ T cells) than standard antiretroviral therapy.[4] Another study showed that raltegravir intensification resulted in a substantial reduction in the viral reservoir of latently infected memory CD4+ T cells (reduction in infectious units per million cells, or IUPM) and in CD8+ T cell activation in patients with viral suppression.[5] However, yet another study showed that the addition of raltegravir to an antiretroviral regimen did not further reduce low-level plasma viremia and found no association between persistence of plasma HIV RNA levels and T cell activation.[6]

One explanation for the seemingly divergent findings with raltegravir intensification may be that its effects are more prominent in gut tissue than in peripheral blood. A number of studies have shown a strong association between cell-based measures of viral persistence and T cell activation in gastrointestinal tissue.[7] As shown in Figure 4, raltegravir intensification reduced immune activation more in gut tissues than in peripheral blood and reduced viral persistence (measured as HIV RNA level) in the terminal ileum.[8]

Ongoing HIV Replication During Antiretroviral Therapy?

Although complete inhibition of viral replication is an unlikely curative strategy for HIV infection, all functional cure strategies are based on first having achieved complete suppression of virus. There are substantial data that indicate HIV replication is not ongoing during suppressive antiretroviral therapy, but there are also data that suggest

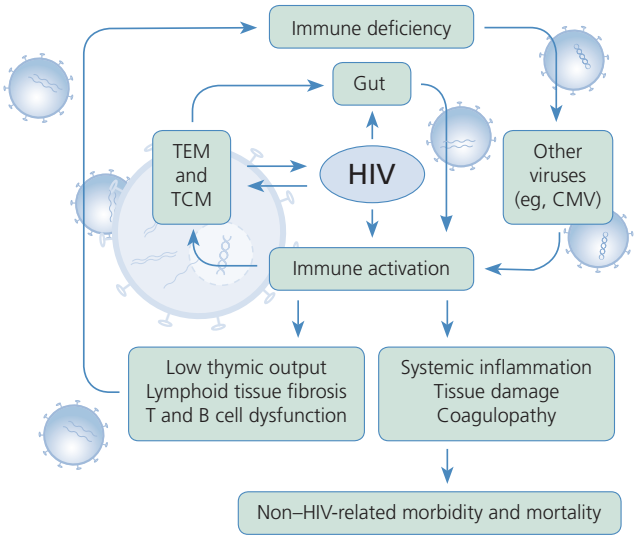

Figure 2. The role of microbial translocation from the gut in fueling immune activation. CMV indicates cytomegalovirus; TCM, central memory T cells; TEM, effector memory T cells. Adapted from Klatt et al.[14]

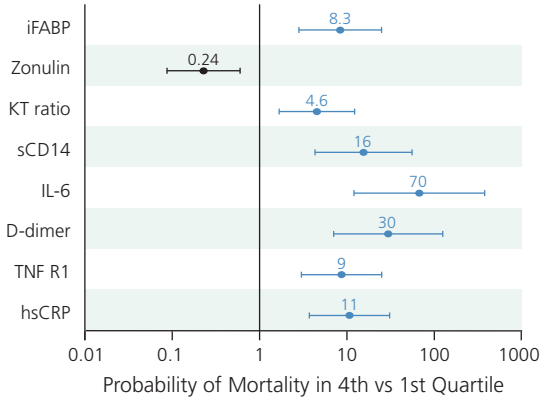

Figure 3. Markers of inflammation and gastrointestinal dysfunction that predict mortality in HIV infection. hsCRP indicates high-sensitivity C-reactive protein; iFABP, intestinal fatty acid binding protein; IL, interleukin; KT, kynurenine-to-tryptophan; sCD14, soluble CD14; TNF R1, tumor necrosis factor receptor 1. Adapted with permission from Hunt et al.[3]

ongoing replication occurs and is associated with immune activation. In determining whether ongoing HIV replication takes place, the source of the sample and the assay used to measure viral reservoir are crucial. Blood tests may indicate the absence of ongoing viral replication, whereas gut or other lymphoid tissue assays that are sensitive enough to detect to 1 viral copy per million cells may demonstrate ongoing replication. Lymphoid tissue is likely the major HIV reservoir in patients on antiretroviral therapy. The gut is actually the largest lymphoid tissue in the body, but widespread destruction of CD4+ T cells in the gut make the lymph nodes or spleen the more likely primary viral reservoir during chronic infection. It is in these tissues that evidence of viral reservoir expansion and resultant ongoing immune activation can be found.

Results of the recently reported VISCONTI (Viro-Immunological Sustained Control after Treatment Interruption) study[9] indicate an association between ongoing viral replication and immune activation. In this study, 14 patients started taking antiretroviral therapy soon after HIV infection and continued it for many years. When antiretroviral therapy was stopped, the patients did not exhibit viral rebound. Like elite controllers, these patients had very low levels of cell-associated HIV DNA. However, unlike elite controllers, who may exhibit immune activation and disease progression, patients in the VISCONTI study had very low levels of T cell activation. A potential implication of these findings is that very early treatment limits the size of the latent viral reservoir, which thus limits the magnitude of immune activation from the outset, potentially providing a lower set point for ongoing inflammation.

Relationship Between HIV-Specific Immunity and HIV Persistence

Ongoing immune activation adversely affects the HIV-specific T cell response, as well as overall CD4+ T cell reconstitution. Thus, ongoing immune activation may interfere with reconstitution of the HIV-specific T cell response. An example of the potential relationship between HIV-specific immunity in the gut and viral persistence is provided in a study by Hatano and colleagues.[10] The study showed that in patients taking antiretroviral therapy, a stronger HIV-specific T cell response in the gut mucosa was associated with lower levels of proviral DNA in peripheral blood mononuclear cells (PBMCs).

Model for Immune Activation and HIV Persistence

If the mechanisms for the association between immune activation and HIV persistence can be identified, it may be possible to direct therapeutic strategies at these mechanisms. Figure 5 shows a potential model for more fully explaining HIV pathogenesis in a way that incorporates persistent immune activation and the role of the viral reservoir in fueling immune activation. Persistent immune activation causes many problems in the immune system, including low thymic output, lymphoid tissue fibrosis, poor immune reconstitution and renewal of CD4+ T cells, and dysfunction of T and B cells. It also continues to cause mucosal damage at the gut surface. These problems can result in immune suppression, with subsequent poor control of pathogens (eg, *Streptococcus*, *Staphylococcus*, herpes viruses), even in patients with low or undetectable HIV RNA levels.

Immune activation affects the reservoir of HIV, even in patients taking antiretroviral therapy. It causes the generation of activated T cells, the target cells for the virus. Cells that are already infected with HIV will proliferate, producing more HIV-infected cells and expanding the viral reservoir. Viral transcription may begin, and some viral replication may occur. There is increasing evidence of the risk of new infection events, even in patients taking fully suppressive antiretroviral therapy. This increase in HIV replication results in further immune activation and, because the patient remains in an immune-suppressed state, poor immune control of newly produced virus. Antiretroviral therapy can profoundly reduce viral replication but does not eliminate residual immune activation nor stop the replication of virus-containing cells or the expansion of the viral reservoir

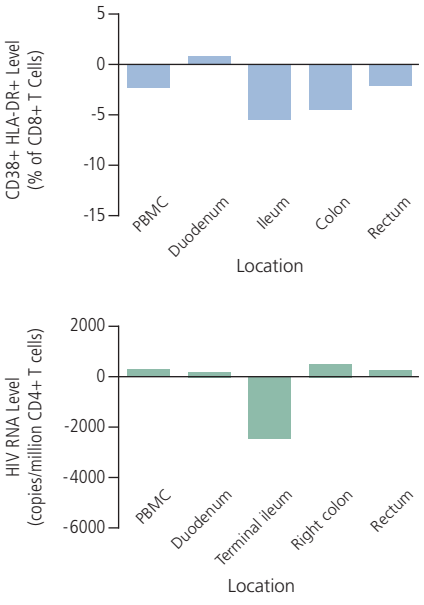

Figure 4. The effects of raltegravir intensification on immune activation (top) and HIV RNA levels (bottom) in peripheral blood mononuclear cells (PBMCs) and gut tissue sites. Adapted from Yukl et al.[8]

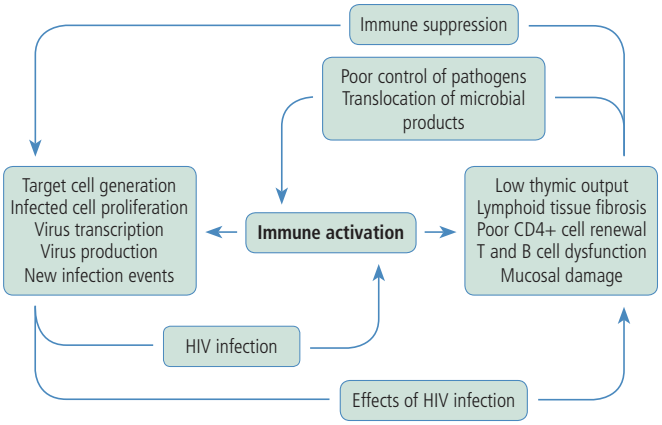

Figure 5. The central role of persistent immune activation in HIV infection. Adapted from Klatt et al.[14]

that can result from persistent immune activation.

Although this picture of pathogenesis may appear daunting with regard to achieving a cure for HIV infection, it actually suggests many points in the processes underlying persistent immune activation that can serve as therapeutic targets. Among the therapeutic interventions in development are chemokine receptor inhibitors, antiinfective therapies, drugs that may reduce microbial translocation, drugs that may enhance T cell renewal, antifibrotic drugs, anti-aging strategies, antiinflammatory agents, and anticoagulants (Table). Combination approaches will likely be necessary to reduce persistent immune activation and counteract its effects in the body, given the multifactorial pathogenesis of HIV infection.

Conclusion: In the Context of a Cure

Numerous mechanisms contribute to HIV persistence, many of which are currently being addressed therapeutically. The unifying theme in these efforts is to reduce the size of the HIV reservoir. Strategies to achieve this include reducing persistent inflammation and increasing immune function, potentially including the strategies of early antiretroviral therapy and antiretroviral therapy intensification. It is also possible that gene therapy could be used to reduce the viral reservoir. It has already been shown that stem-cell transplants can lead to a reduction in the size of the viral reservoir (ie, in the Berlin patient[11]), serving as proof of principle that such genetic approaches may be viable. Drugs with biologic activity against latent virus exist and are being assessed, and vaccines may be developed to enhance host clearance mechanisms (ie, by boosting the damaged HIV-specific immune response). As noted, a combination of approaches will be necessary to address the many aspects of HIV infection and persistent immune activation.

Table. Therapeutic Interventions in Development to Reduce Persistent Immune Activation

Intervention	Examples
Antiinfective therapy	Cytomegalovirus, Epstein-Barr virus, herpes simplex virus, HCV/HBV
Antiaging	Caloric restriction, sirtuin activators, vitamin D, omega-3 fatty acids, rapamycin, diet, exercise
Enhance T-cell renewal	Growth hormone, interleukin 7
Chemokine receptor inhibitors	Maraviroc, cenicriviroc
Microbial translocation	Sevelamer, colostrum, rifaximin
Antifibrotic drugs or agents	Pirfenidone, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, keratinocyte growth factor
Anticoagulants	Low-dose warfarin, dabigatran, aspirin, clopidogrel
Antiinflammatory drugs	Chloroquine, hydroxychloroquine
	Minocycline
	NSAIDs: COX-2i, aspirin
	Statins
	Methotrexate
	Thalidomide, lenalidomide, pentoxyfyline (weak TNF inhibitors)
Biologics	TNF inhibitors, interleukin 6 inhibitors, anti–alpha-interferon antibodies, anti-PD1 antibodies

COX-2i indicates cyclooxygenase-2 inhibitor; HCV, hepatitis C virus; NSAID, nonsteroidal antiinflammatory drug; PD1, programmed death 1; TNF, tumor necrosis factor.

Presented by Dr Douek in March 2013. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Douek in October 2013.

Financial Affiliations: Dr Douek has no relevant financial affiliations to disclose.

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Perspective

Linkage, Engagement, and Retention in HIV Care Among Vulnerable Populations: "I'm Sick and Tired of Being Sick and Tired"

There are disparities in engagement and retention in HIV care and outcomes of care across segments of society. For example, HIV mortality rates remain markedly elevated among black women and men compared with their white counterparts. These differences reflect broader disparities across social, economic, and cultural lines. Improvement in engagement and retention in HIV care requires interventions that account for forces present in the socioecologic framework of health behaviors. Improvement in linkage to care at HIV testing is crucial to overall engagement and retention in care. Strategies for linkage to care at testing can help overcome many of the forces that result in failure to engage and remain in care by starting the patient on a solid path to clinical care. This article summarizes a presentation by Victoria A. Cargill, MD, MSCE, at the IAS–USA continuing education program held in New York, New York, in May 2013.

Keywords: *HIV care disparities, linkage to care, socioecologic framework, engagement and retention in care, practitioner behavior*

"I Don't Want To Go to the Hospital"

Patient A is a 34-year-old African American woman who tested positive for HIV infection at 19 years of age. She has given birth to 4 HIV seronegative children, but her first child died at age 6 months due to crib death and another (one of a set of fraternal twins) died at age 9 years from sickle cell crisis. Patient A dropped out of care for 9 years and has since been intermittent in her treatment follow-up. She is nonadherent to medications and appointments. Her mother brought her to the clinic, where she presented with a 70 lb weight loss, thrush, fever, cough, tachypnea, and diarrhea. She stated, "I don'twant to go to the hospital."

Syndemics of Disparities

The above scenario is unfortunately all too common. Since 1985, more than 27 antiretroviral drugs have been approved for use in the United States, an indicator of the progress that has been made in HIV therapy. Unfortunately, all segments of society have not equally benefitted from this progress. At the same time that the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) data have highlighted the increased life expectancy of HIV-infected patients starting antiretroviral therapy,[1] the WIHS (Women's Interagency HIV Study) data reemphasize that black HIV-infected women are twice as likely to die with AIDS as their white counterparts.[2]

Overall, Latinos and blacks are substantially more likely to present late for care and experience higher morbidity and mortality than other population groups. Persons dying with HIV infection increasingly are women, blacks/African Americans, residents of the US South, and individuals aged 45 years or older. HIV infection remains one of the leading causes of death among persons aged 25 years to 44 years in the United States, particularly among blacks/African Americans.

As shown in Figure 1 (top), although there have been marked reductions in annual mortality from HIV disease in the United States since 1996 among all racial and ethnic groups, the rate in black/African Americans remains strikingly elevated.[3] Figure 1 (bottom) shows the disparity when mortality rates for black men are compared with those for white men by age group.[4]

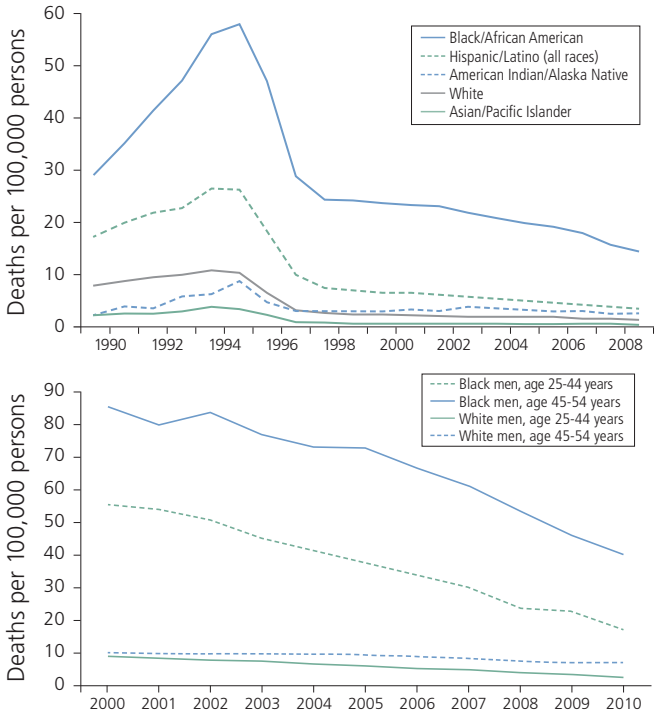

Figure 1. Age-adjusted HIV-related death rates by race and ethnicity (top). Rates are standardized on the age distribution of the US population in 2000. Adapted from National Center for HIV/AIDS.[3] HIV-related death rates in black men and white men by age group (bottom). Adapted from National Vital Statistics System.[4]

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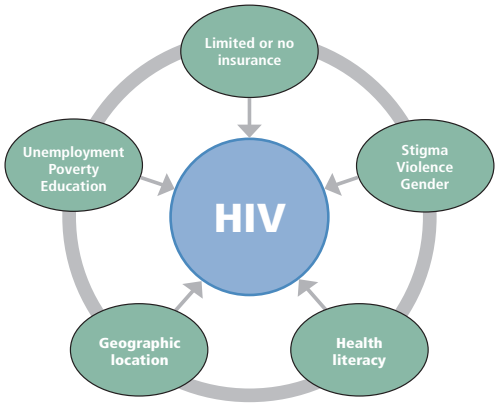

Figure 2. HIV infection: A single factor among many potential socioecologic disparities.

HIV infection presents as a health disparity but is only one disparity among many that affect both the quality and quantity of life among the vulnerable populations in society (Figure 2). These disparities overlap and intersect to present a web of challenges for many racial and ethnic minorities living with HIV infection and those who provide care for them.

Poverty is one such disparity. Poverty rates for blacks and Hispanics exceed the national average. According to National Poverty Center data, 27.4% of blacks and 26.6% of Hispanics are poor, compared with 9.9% of non-Hispanic whites and 12.1% of Asians.[5] Foreign-born noncitizens in the United States also have high poverty rates.[5]

Health illiteracy and limited or nonexistent health insurance coverage negatively impact the management of HIV infection and are particularly relevant to vulnerable and marginalized populations in that health literacy can be correlated with HIV knowledge[6] and HIV treatment adherence.[7] However, the impact of low health literacy can be moderated by self-efficacy[8]—namely, people's belief that they can take control in their lives to improve their circumstances. Among individuals with self-efficacy, the impact of low health literacy is not as profound.

Several large studies on health insurance coverage have demonstrated an association between earlier initiation of antiretroviral therapy[9] and having commercial or private insurance. Although less striking, a similar association has been found between antiretroviral therapy initiation and having Medicare coverage. Individuals enrolled in Medicaid consistently initiated antiretroviral therapy at a more advanced stage of disease, corrobrating earlier findings.[9,10] Health insurance coverage is also correlated with employment, and unemployment rates are much higher for blacks and Latinos. The unemployment rate for blacks was twice that for whites in 2012—a ratio that has not changed since the US Beareau of Labor Statistics began reporting unemployment by race in 1972.[5]

Along with poverty, unemployment, underemployment, and limited health literacy, violence must be included as a factor that can negatively affect HIV care. Violence and suicide rates are disproportionately higher in racial and ethnic minority populations. Native Americans have the second-highest rate of suicide across all age groups. Blacks account for 48.7% of homicide deaths, which is the highest rate for any population group, and more than half of these deaths occur in men aged 15 years to 34 years. Native Americans rank second in homicide deaths, followed closely by Hispanics.[11]

In addition to these disparities, many other factors may affect an individual's ability to access and remain in health care, including:[12]

- Stigma
- Homophobia
- Language barriers
- Incarceration
- Shame
- Privacy concerns
- Distrust of practitioners
- Active substance use
- Unstable housing
- Limited education
- Isolation
- Lack of support
- Fear of disclosure
- Mental health status

Moving Beyond the Individual—A Socioecologic Framework

Correcting the disparities in HIV care and the differential outcomes for the marginalized and vulnerable sectors of society will require addressing the larger sociocultural context in which these individuals live. Thus, examining the socioecologic framework in which individuals participate allows for an examination of and accounting for the external factors that influence individuals at interpersonal, organizational, community, and public policy levels—all of which can impact HIV care–seeking behavior, as well as an individual's general knowledge, attitudes, and skills. The socioecologic approach has been particularly useful in addressing health behaviors that are influenced by factors such as culture, trust, and beliefs, with prenatal care and weight loss interventions being prime examples.

Mugavero and colleagues have provided a detailed picture of the socioecologic framework for HIV care in which they demonstrate the complex multilevel factors that can affect an individual's engagement in care (Table).[13] For example, at the individual level, there are numerous factors, such as age, sex, race, and ethnicity, that may predispose patients not to engage or remain in care. But there are also enabling factors that may tend to keep them engaged, including health insurance, transportation, social support, self-efficacy, and resiliency (ie, the ability to navigate barriers inherent to seeking and engaging in care). Relationships with case managers, health care practitioners, and social networks, for example, can facilitate or impede engagement in care.

"Are You Sure I'm HIV-Positive?"

Patient B is a 35-year-old African American man who describes himself as a "player." He also has a known factor VIIa deficiency. Four weeks before presentation to clinic, he was treated for syphilis and was encouraged to undergo HIV testing. His rapid HIV test was positive, as was confirmatory

Table. Sociologic Factors in HIV Care

Policy	Health Care System	Community	Relationships	Individual
■ HIV testing guidelines ■ HIV treatment guidelines ■ Quality measures ■ Best practices ■ Workforce ■ Reimbursement ■ Funding - CDC - Health departments - CMS - SAMHSA - HRSA Ryan White (distribution of funds; ADAP) - Coordination	■ Surveillance ■ Testing services ■ Prevention services ■ Medical services ■ Supportive services ■ Service integration ■ HIV clinic distance ■ HIV clinic culture ■ Appointment availability ■ Medical home	■ Neighborhood ■ Poverty ■ Education ■ Social norms ■ Stigma ■ Employment ■ Corrections facilities	■ Intimate partners ■ Family members ■ Friends ■ Social networks ■ Medical provider ■ Case manager ■ Mental health provider ■ Peer mentor/navigator ■ Relationship factors - Trust - Communication - Longevity - Compatibility	■ Potential predisposing factors - Age - Race - Ethnicity - Sex - Mental health - Substance use ■ Perceived needs - Health benefits - Symptoms - Comorbidities - Past experiences ■ Potential enabling factors - Insurance coverage - Transportation - Housing - Income - Education - Social support - Empowerment - Self-efficacy - Spirituality - Coping skills - Resiliency

ADAP indicates AIDS Drug Assistance Program; CDC, Centers for Disease Control and Prevention; CMS, Centers for Medicare and Medicaid Services; HRSA, Health Resources and Services Administration; SAMHSA, Substance Abuse and Mental Health Services Administration. Adapted from Mugavero et al.[13]

testing. Posttest counseling included a discussion about the meaning of a positive test result, the importance of getting into care, the role of barrier protection in sexual safety, and the need for cleansing of any drug equipment or sex toys. He was given a list of treatment sites, with those closest to his stated address circled. He never showed up at any of the treatment sites—another common scenario.

Engagement in HIV Care

Failure to follow up after HIV testing is a common scenario in the HIV care cascade. As discussed below, several studies have convincingly demonstrated that engagement in HIV care *begins at the testing site.* How closely the HIV counseling, testing, and referral (CTR) experience correlates with subsequent linkage to care appears to be related to the tone and expectation for future engagement in care established during CTR. The Never in Care Project conducted in 5 locales with mature HIV epidemics (New York City, Philadelphia, and sites in Indiana, Washington state, and New Jersey) highlights the importance of this experience.[12] HIV-infected individuals who never sought care beyond testing were predominantly male (71%) and African American (54%), with almost half being younger than 30 years. Dissatisfaction with the CTR experience was a pervasive theme. Some of the factors reported were lack of empathy, insufficient counseling, and incorrect information. Being given the wrong address for a practitioner discouraged some individuals from pursuing care. One 25-year-old African American man stated, "They acted like they could not have cared less. It's a good thing I have support. And if you think this means I'm going to go back and see anyone about this, I won't. No. Never. Never."[12]

The method of referral also had an effect on linkage outcomes. Passive referral in the form of a card, brochure, or verbal direction was often perceived as constituting little or no help. Patients receiving passive referral were less likely to go to a treatment location. Active referral in which the tester made the treatment appointment or accompanied the patient was associated with a feeling of support and a higher likelihood of follow through. One patient reported, "When they did the quick test she gave me her card, she talked to me and my mom then.... Not knowing if I would have that support group, she made herself a support group [for me] until I could get to the [AIDS service organization]."[12] Such challenges are part of the rationale for test-and-treat interventions presently being devised, tested, and implemented in a number of settings.

Practitioner behavior is a crucial piece of the engagement and retention puzzle. A number of earlier studies suggested that antiretroviral prescribing was racially biased,[14,15] but repeat studies have failed to corroborate this finding.[16,17] It is clear, however, that patient trust in the practitioner is an important component of care adherence in some populations, including African Americans,[18] as emphasized by recent data confirming the importance of practitioners to engagement in HIV care.[19] In an urban clinic, more than 1300 patients rated their communication and relationships with their HIV practitioners. Appointment adherence correlated with patients' perceptions

that they were being treated with dignity and respect, as well as with the opinion that the practitioner listened to their concerns. Patients also kept more appointments if practitioners explained things in a way that they could understand and took the time to get to know them as individuals. Being involved in decision making was not associated with appointment adherence.[19]

Beyond improving practitioner and patient interactions, other strategies that can help improve engagement and retention in care include:

- *Easing of Structural Barriers*. Small changes, such as increasing clinic hours, ensuring appointment availability, etc.
- *Novel approaches for specific populations.* STYLE (Strength Through Youth Livin' Empowered) is a Health Resources and Services Administration (HRSA)-funded project that uses social media as a way to reach young black and Latino men who have sex with men.[20]
- *Easy, low-effort interventions.* Use of brochures, posters, and messages conveying the importance of regular clinic attendance in an urban clinic yielded modest (7%) but consistent improvement in follow-up.[21]
- *Incentives.* Cab vouchers, grocery cards, other inducements to adhere to appointments.
- *Peer navigators.* Peer navigators have been successfully used in a model to increase access to and retention in dental care through help with care coordination and support.[22]
- *Medical homes.* HRSA is also interested in developing patient-centered medical homes with retention specialists, staff training, and a variety of programs to increase reengagement. In one study, the retention specialist alone was directly responsible for the return of 116 (16.2%) of 716 reengaged patients.[23]
- *Multidisciplinary teams.* Multidisciplinary team approaches have been used for antiretroviral therapy adherence and primary HIV care, with teams often including a case manager, social worker, pharmacist, nurse, and care practitioner.[24]

Moving Forward—What We Need

In the simplest terms, what is needed to enhance linkage from testing into HIV care can be described as the 4 Es: Easy, Evidence-based, Economical, and Effective interventions targeted to specific populations at increased risk for care disengagement, including youth, minorities, and lower-literacy populations.[25] Robust clinical trials of real-world interventions to enhance care linkage, facilitate patient-practitioner communication, build system navigation skills, and encourage reengagement in care for at risk populations continue to be needed, as interventions that work for one population group may not be applicable to another. Enhanced safety nets to quickly identify and engage individuals who do not link to care after testing are needed, as is recognition that, sadly, not everyone can be engaged.

For the HIV practitioner, losing patients despite one's best efforts is an unfortunate and bitter reality. As noted above, patient A refused hospitalization. The practitioner asked the patient's mother to call family members to the office, which led to a gathering of 14 people, including the patient's extended family. Her issues were discussed, and a case manager assured her that her children would not be prevented from seeing her if she were hospitalized. Her mother, who had custody of her children, and her uncle also promised to ensure that her children would be able to visit during her hospitalization. An adherence team member offered to accompany her to the hospital, to which she agreed. Unfortunately, she was so debilitated and emaciated that she was unable to walk, so the practitioner carried her from the room to the waiting stretcher. She was hospitalized and treated for bacterial pneumonia, and antiretroviral therapy and opportunistic infection prophylaxis were initiated. At discharge, her CD4+ cell count was 2/µL and her plasma HIV RNA level was in excess of 375,000 copies/mL.

However, 6 months later, she was nearly unrecognizable—she had gained 20 lbs, her viral load was undetectable, and her CD4+ cell count was 200/µL. She was wearing makeup and appeared to be well on her way to better health. But 8 months later, just 14 months from the time of her last hospitalization, she dropped out of care. Thus, the cycle begins again—a cycle we very much need to stop.

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Perspective

Implications of the Affordable Care Act for People With HIV Infection and the Ryan White HIV/AIDS Program: What Does the Future Hold?

There are numerous aspects of the Patient Protection and Affordable Care Act that will be important for people in the United States with HIV infection, including consumer protections and private insurance reforms, establishment of health care marketplaces in every state, new benefit standards, Medicare fixes, prevention enhancements, expansion of Medicaid, and health system improvements. However, it is unlikely that these changes will address all the needs of people with HIV infection in the United States. The Ryan White HIV/AIDS Program will thus remain crucial for the provision of adequate health care to HIV-infected individuals, but it will need to change. Changes in the role of the Ryan White HIV/AIDS Program will depend largely on state decisions on Medicaid expansion and health care marketplaces. This article summarizes a presentation by Jennifer Kates, PhD, at the IAS–USA continuing education program held in New York, New York, in April 2013.

Keywords: *HIV, Patient Protection and Affordable Care Act, PPACA, ACA, Ryan White Program, health insurance, exchanges, marketplaces, state health care, Medicaid*

More than 30 years into the HIV epidemic, there are now more than 1 million people in the United States living with HIV. The number of new HIV infections has remained relatively stable for more than a decade at approximately 50,000 new infections per year, although new infections are rising among men who have sex with men. People with HIV infection are more likely than the overall US population to be low-income and uninsured and to rely heavily on Medicaid for insurance coverage.[1-3]

However, the Centers for Disease Control and Prevention (CDC) estimates that close to two-thirds (63%) of people with HIV infection are not retained in care, only 33% are taking antiretroviral therapy, and only 25% are virally suppressed, despite new data indicating that early initiation of antiretroviral therapy not only has tremendous clinical benefit but also substantially reduces the risk of HIV transmission. These findings have pointed to the real possibility of achieving an AIDS-free generation, if more people with HIV infection can be engaged and retained in care (Figure 1).[4,5]

Implications of the Affordable Care Act for People with HIV Infection

There are numerous aspects of the Patient Protection and Affordable Care Act, commonly referred to as the Affordable Care Act (ACA), that will be important for people with HIV infection, including consumer protections and private insurance reforms, health care marketplaces in every state, new benefit standards, Medicare fixes, prevention enhancements, expansion of Medicaid, and health system improvements.

The consumer protection and private insurance reforms provisions put an end to lifetime and annual coverage limits, eliminate exclusions for preexisting conditions, prohibit insurers from rescinding coverage, and extend eligibility for dependent coverage to up to 26 years of age. Under the ACA, health plans can no longer charge higher premiums to individuals with preexisting conditions and cannot discriminate against individuals on the basis of sexual orientation or gender identity.

The ACA will require most individuals to have health insurance by 2014. To help achieve this goal, health care marketplaces, also called exchanges, where individuals and small businesses may purchase coverage, will be created in every state. These state-based marketplaces are intended to create a more organized and competitive

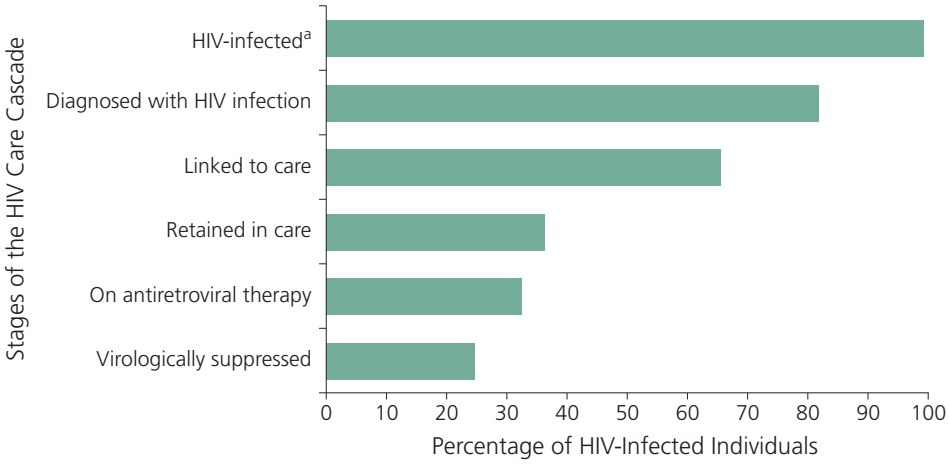

Figure 1. The proportion of individuals at each stage of the cascade of HIV care in the United States. Adapted from Centers for Disease Control and Prevention and Kaiser Family Foundation.[4,5] [a]Includes individuals who are unaware of their HIV infection.

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insurance market. They must offer a choice of qualified health plans (those certified by each marketplace and that meet any other specified requirements) and provide information to consumers about the offerings of each plan. To make coverage in the marketplaces more affordable, the ACA includes provisions that lower insurance premiums and cost-sharing obligations for those individuals or families with lower incomes. Tax credits will be available to those with incomes between 100% and 400% of the federal poverty level; in 2013, the federal poverty level is defined at $11,490 for individuals and $19,530 for a family of 3.[6] In addition, those with incomes between 100% and 250% of the federal poverty level will also be eligible for cost-sharing subsidies through lower deductibles and copayments. States can choose to run their own marketplace, do so in partnership with the federal government, or choose to default to a fully federally run marketplace.

Many more states than anticipated reportedly intend to default to federal health insurance marketplaces (27 states), thus the federal government will be responsible for the operation of health care marketplaces in the majority of states (Figure 2).[7] Seven states have indicated that they intend to partner with the federal government to run their marketplace, and 16 states, plus the District of Columbia, will run their own marketplaces.

Qualified health plans that will participate in state health care marketplaces are in the process of setting up their provider networks now. As required by the health reform law, qualified health plans must include what are termed essential community providers, those providers who primarily serve low-income and underserved communities; Ryan White HIV/AIDS Program providers have been included in this definition. However, although states must ensure that networks include a certain share of essential community providers, they do not have to seek out community providers from all sectors. Thus, it will be important for Ryan White HIV/AIDS Program providers and other HIV-focused essential

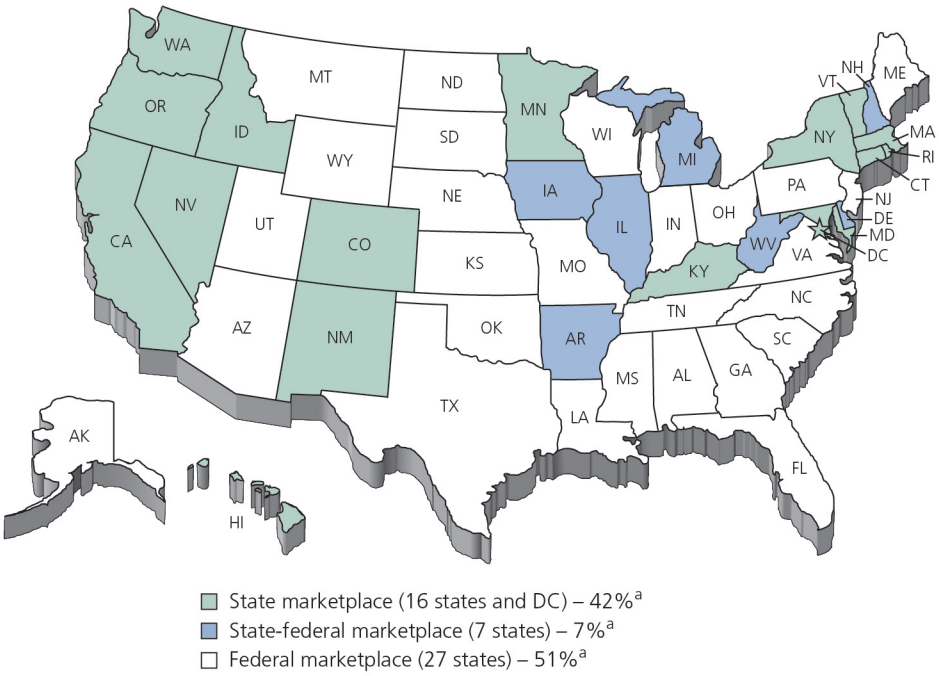

Figure 2. State-by-state decisions to date on the implementation of Patient Protection and Affordable Care Act health insurance marketplaces. Adapted from Kaiser Family Foundation and Centers for Disease Control and Prevention.[7,9] [a]Estimated percentage of HIV-infected individuals living in these states.

community providers to proactively engage with the new marketplaces in their states and work to become part of qualified health plan networks, efforts that should be undertaken now.

With regard to benefit standards, the ACA mandates that all new individual and group health plans sold inside and outside state marketplaces include Essential Health Benefits (EHB), a comprehensive set of services across 10 categories. Individuals newly eligible for Medicaid in states that choose to expand Medicaid must also be provided EHB coverage. The 10 EHB categories consist of ambulatory patient services; emergency services; hospitalization; maternity and newborn care; mental health and substance use disorder services, including behavioral health treatment; prescription drugs; rehabilitative and habilitative services and devices; laboratory services; preventive and wellness services and chronic disease management; and pediatric services, including oral and vision care. The final rule for coverage of prescription drugs is that plans must cover "at least the greater of" 1 drug from every US Pharmacopeia category and class or the same number of prescription drugs in each category and class as the EHB benchmark, which is crucial in combination antiretroviral therapy because more than 1 drug is used in category and class. Plans must also have procedures in place "that allow an enrollee to request and gain access to clinically appropriate drugs not covered by the health plan."

Beyond this and other requirements, states have been given the flexibility to choose a benchmark plan to use as a standard for determining the scope of EHB coverage. Therefore, it will be important for practitioners and other patient advocates to assess whether health plans include all the HIV-related medications and other benefits needed to enable HIV-infected patients to receive appropriate care. Preliminary analysis indicates that most benchmark plans chosen by states go beyond the minimum required by law and include most antiretroviral drugs.[8]

The ACA also made important changes to Medicare. First, by 2020, the ACA will close the Medicare prescription drug gap (or "donut hole") currently impacting all Medicare Part

D beneficiaries. This donut hole is the gap in Medicare Part D coverage during which beneficiaries must pay out of pocket (true out-of-pocket [TrOOP] costs) for medications until they reach the catastrophic level when Medicare drug coverage begins again. Second, and more specific to HIV-infected individuals, prior to the ACA, spending by the AIDS Drug Assistance Program (ADAP) for Part D beneficiaries in the donut hole did not count toward their TrOOP costs; the ACA changed this, as of 2011, permitting ADAP spending to count toward TrOOP, thus allowing ADAP dollars to extend further.

There is considerably more emphasis on prevention under the ACA than there has been in the health care system in the past. The ACA requires that all new health plans provide certain preventive services at no cost, including those services rated A or B by the US Preventive Services Task Force (USPSTF). Medicare must also provide such services at no cost, and newly eligible Medicaid beneficiaries, in states that expand Medicaid, must also receive these services at no cost. Traditional state Medicaid programs, for those already eligible, are not required to cover these services, but the federal government will pay a 1% increase in the Federal Medical Assistance Percentages (FMAPs) for these services to states that provide them at no cost to Medicaid beneficiaries. Routine HIV screening received an A rating by the USPSTF in April 2013, and annual HIV counseling and testing for sexually active women are now offered free of charge.

One of the most important health reforms for people with HIV infection is the expansion of Medicaid. As of January 2014, the law expands Medicaid eligibility to nearly all low-income individuals and establishes an eligibility floor of 138% of the federal poverty level (approximately $16,000 annual income for an individual and $27,000 for a family of 3, in 2013). Previously, individuals had to be both low-income and categorically eligible (eg, disabled, a pregnant woman, a senior) to qualify for Medicaid in their state. For many low-income people with HIV infection, this change eliminates a catch-22 situation in which they could not qualify for Medicaid and receive antiretroviral treatment through the program until they were categorized as disabled, despite the fact that antiretroviral therapy may help prevent this kind of disability. The law also provides enhanced FMAPs to states and will cover the full cost of the expansion from 2014 to 2016, before scaling down to cover 90% of the cost in 2020 and thereafter.

A ruling by the US Supreme Court in June 2012, however, while upholding the Medicaid expansion (and the rest of the ACA), limited the authority of the Department of Health and Human Services (DHHS) Secretary to enforce the expansion, effectively making expansion of coverage a state option. There are currently 25 states, plus the District of Columbia, that have indicated they will move forward with expansion and 25 states that have indicated they will not move forward (Figure 3).[7,9] Approximately 57% of people with HIV infection live in states that have indicated they are expanding Medicaid and approximately 43% live in states that indicate they are not expanding. Many southern states oppose expansion, and it is in southern states that HIV care infrastructure and access are often weakest. States can choose to expand Medicaid at some point in the future (the Supreme Court decision effectively removed the requirement that they must do so as of 2014), allowing states to continue to debate into the coming years whether they support or oppose Medicaid expansion.

Notably, there were several health system improvements under the ACA that may help people with HIV infection, including the creation of Medicaid Health Homes for people with chronic conditions; increased Medicaid payments for primary care physicians and subspecialists in 2013 and 2014, with ongoing discussion about extending the duration of these provisions; and new investments in community health centers, which serve many HIV-infected people.

Implications for the Ryan White HIV/AIDS Program

Insurance coverage alone does not ensure access to or receipt of care. The Ryan White HIV/AIDS Program acts as a national safety net for people with HIV infection, filling gaps in care not

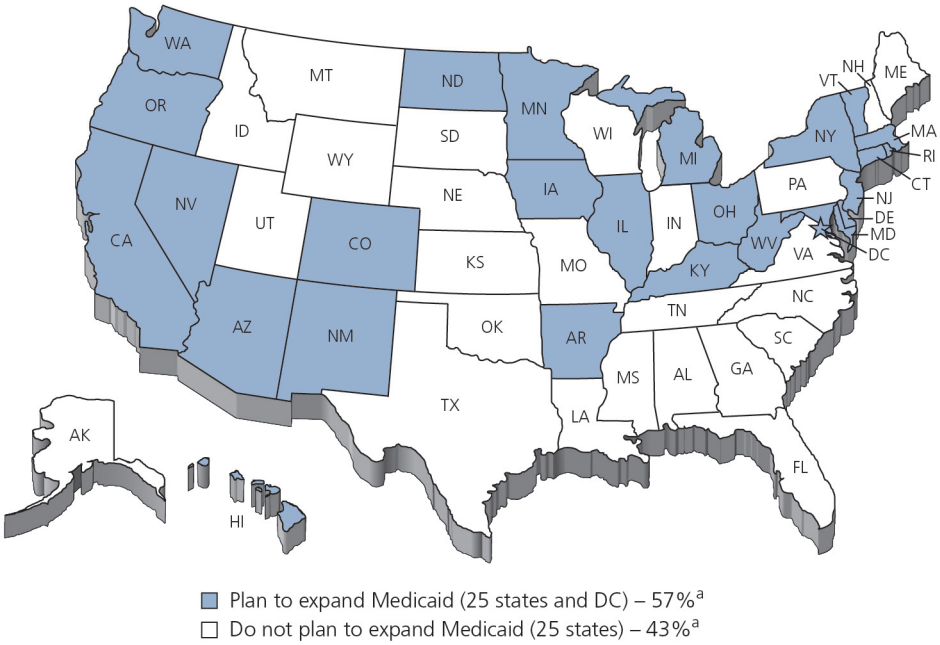

Figure 3. State-by-state decisions to date on whether they intend to expand Medicaid. Adapted from Kaiser Family Foundation and Centers for Disease Control and Prevention.[7,9]
[a]Estimated percentage of HIV-infected individuals living in these states.

covered by other resources and serving as a payer of last resort. In fact, most clients in the Ryan White HIV/AIDS Program today are insured and use the Program to supplement or complete their coverage.[10] Although the ACA is expected to expand coverage to many people with HIV infection, it is also expected that the Ryan White HIV/AIDS Program will still be needed to provide comprehensive, quality HIV care and to help engage and retain HIV-infected patients in that care. There are many crucial HIV-related services provided by the Program that are not typically covered by insurance plans, such as assistance with treatment adherence and case management (Figure 4).[5]

An example of how the role of the Ryan White HIV/AIDS Program may change can be seen in the evolution of health coverage in Massachusetts, which began major coverage expansions more than a decade ago and now has near universal health coverage. Even with this expanded coverage in Massachusetts, the Ryan White HIV/AIDS Program has remained crucial. An increasing share of Program funding has paid for premiums and copayments to engage and retain HIV-infected patients in care in the state. Massachusetts has reported a reduction in new HIV diagnoses, very high care-retention rates, and high rates of viral suppression, results that it attributes to coverage expansions and the Ryan White HIV/AIDS Program, among other factors.[11]

Ultimately, the impact of the ACA on the Ryan White HIV/AIDS Program will depend largely on state decisions, particularly concerning Medicaid expansion but also the scope of benefits in their marketplace plans. As seen in the state of Massachusetts, a greater share of Program funding may be used to assist clients in paying for new coverage in state marketplaces and in completing that coverage where there are limits. Ryan White funding will still be needed to assist people with HIV infection in traditional Medicaid programs who may continue to face benefit limits as they do today. Moreover, the Ryan White HIV/AIDS Program will be crucial for people with HIV infection who live in states that do not choose to expand Medicaid (Figure 3). Lastly, the Program will continue to be an important source of care and services for HIV-infected immigrants, because undocumented persons are not eligible for Medicaid or health insurance marketplaces and newly legal residents have a 5-year waiting period before Medicaid eligibility.

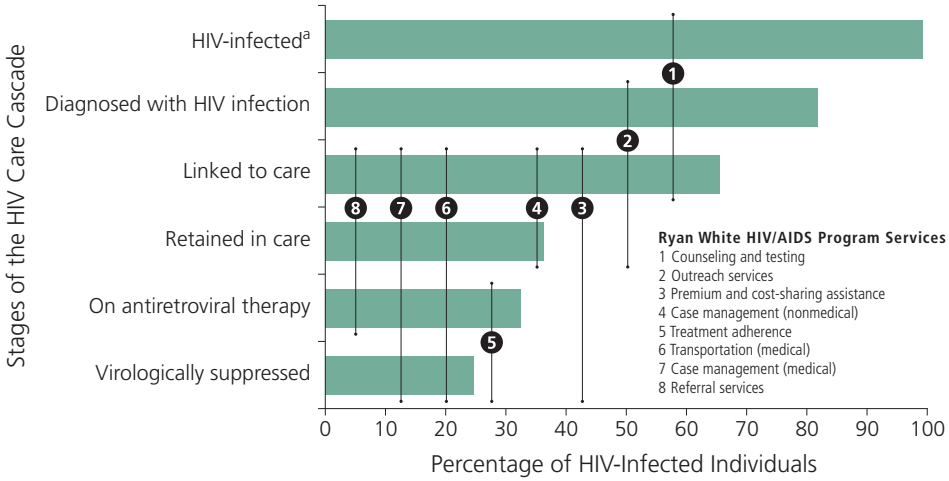

Figure 4. Supporting role of the Ryan White HIV/AIDS Program across the HIV care cascade in the United States. Adapted from Centers for Disease Control and Prevention and Kaiser Family Foundation.[4,5] [a]Includes individuals who are unaware of their HIV infection.

Program practitioners have an important role to play in helping clients, through education and guidance, maximize opportunities to obtain new coverage. In some cases, Program practitioners may receive funding to become Patient Navigators who will play a key role in helping individuals to access coverage. Practitioners may also join Medicaid and marketplace provider networks. However, as mentioned above, Program practitioners must seek out such opportunities proactively. It is also important to note that the payer-of-last-resort requirement will still be in place for the Ryan White HIV/AIDS Program and that Program funds may not be used "for any item or service to the extent that payment has been made or can reasonably be expected to be made."

The Ryan White HIV/AIDS Program, first authorized in 1990, has been reauthorized by the US Congress 4 times, most recently in 2009. Although its current authorization ended on September 30, 2013, reauthorization is not required for the Program to continue, as long as funding is provided by Congress through annual appropriations. Discussions about the future role of and potential changes to the Program have already begun, but there are still many uncertainties about how the ACA will affect it, particularly given state decisions on Medicaid expansion. These uncertainties have led some to question what the most appropriate timing for reauthorization of the Ryan White HIV/AIDS Program might be.

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